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JENKINS, WILSON, TAYLOR & HUNT, P. A.
3100 TOWER BLVD., Suite 1200
DURHAM, NC 27707

EXAMINER
MARVICH, MARIA

ART UNIT	PAPER NUMBER
1633	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/501,756	LI ET AL.	
	Examiner	Art Unit	
	Maria B. Marvich, PhD	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 September 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-119* is/are pending in the application.

4a) Of the above claim(s) *32-119* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-31* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *16 July 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *3/29/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-119 are pending.

Election/Restrictions

Applicant's election without traverse of Group I (claim 1-31) in the reply filed on 9/18/07 is acknowledged. Claims 32-119 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected subject matter, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 9/18/07.

Claim Objections

Claims 1 and 13 are objected to because of the following informalities: claim 1 recites "A recombinant adenovirus comprising an adenovirus". However, the adenovirus cannot comprise an adenovirus but an adenovirus. It would be remedial to delete "comprising an adenovirus". As well, claim 1 recites, "the one or more AAV REP78/68 polypeptides is inducibly expressed". For grammatical correctness it would be remedial to recite --are inducibly expressed--. This is similar to the case in claim 13 which should recite --are constitutively expressed-- for grammatical consistency.

Claims 2, 7 and 18 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claim 1 is drawn to a recombinant adenovirus that

encodes one or more AAV REP78/68 polypeptides and claim 2 to the recombinant adenovirus of claim 1 that encodes one or more AAV REP78/68 polypeptides following serial passage. The recombinant adenovirus of claim 1 is no different then that of claim 2 and therefore, claim 2 does not further limit claim 1. Claims 7 and 18 are drawn to a recombinant adenovirus of claim 1 encoding the one or more AAV REP78/68 peptides operably linked to an inducible promoter. Claim 1 inherently comprises such a nucleic acid as claim 1 encodes one or more AAV REP78/68 peptides in which the peptides are inducibly expressed. Claim 13 inherently comprises nucleic acid encoding AAV REP 52/48 in which the peptides are constitutively expressed. Hence, the adenovirus of claim 1 must comprises a nucleic acid encoding the one or more AAV REP78/68 peptides operably linked to an inducible promoter and the adenovirus of claim 13 must comprises a nucleic acid encoding the one or more AAV REP52/64 peptides operably linked to a constitutive promoter. This is distinct from the case in claim 21 and 28 wherein the recombinant adenovirus comprises viral capsids as well as nucleic acids encoding these viral capsids as 1) the viral capsid can be assembled *in vitro* and 2) claim 21 does not stipulate that the viral capsids are encoded by the virus.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claim 31 is rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. The term "host cell" defined by the specification at page 33, line 7-12 states that the cell is *in vitro* or *in vivo*. The scope of the claims therefore encompasses a

human being, which is non-statutory subject matter. As such, the recitation of the limitation "non-human" or "isolated" would be remedial. See 1077 O.G. 24, April 21, 1987.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-31 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims are vague and indefinite in that the metes and bounds of REP78/68 are unclear. The recitation REP78/68 polypeptides appear to intend REP78 and REP68 peptides. Alternatively, the notation could refer to a fusion of the two or the two peptides in the alternative. Nonetheless, by recitation of REP78/68 it is not clear whether applicants intend that both peptides, the peptides in the alternative or a fusion protein are encoded by the genome. This is further complicated by the recitation in dependent claims such as claim 4 "the one or more REP78/68 polypeptides comprises a REP78 polypeptide, a REP68 polypeptide, or a combination thereof" which supports all three interpretations. However, the biology of AAV does not support an interpretation of an adenovirus that encodes one or the other. Nucleic acid encoding the REP78 and REP 68 peptides is under control of the p5 promoter wherein a single transcript for both peptides is produced. Alternative splicing leads to production of REP 78 and REP 68. The specification does not describe a vector in which one or the other are produced. As well, the specification does not teach production of a fusion of REP78/68. Therefore, it appears that

REP78/68 is a notation for both REP 78 and REP 68. If so it would be remedial to amend the recitations of "REP 78/68" to read --REP 78 and REP 68--.

Claim 15 recites the limitation "the one or more REP52/48 polypeptides" in claim 10. There is insufficient antecedent basis for this limitation in the claim. For purposes of examination, claim 15 will be considered to depend form claim 13,

Claim Rejections - 35 USC § 112, first paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-31 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an adenovirus that encodes REP 78 and REP 68 and optionally REP 52 and REP48 and VP-1, VP-2, VP-3 wherein the sequence encoding these proteins are SEQ ID NO: 1, 3, 5 and 8 and encode SEQ ID NO: 2, 4, 6, 7 and 9-11 wherein when REP78/68 is under control of hsp70, the promoter is SEQ ID NO:14, does not reasonably provide enablement for any other embodiment. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

The test of enablement is whether one skilled in the art could make and use the claimed invention from the disclosures in the patent coupled with information known in the art without undue experimentation (*United States v. Telectronics, Inc.*, 8 USPQ2d 1217 (Fed. Cir. 1988)). Whether undue experimentation is required is not based on a single factor but is rather a

conclusion reached by weighing many factors (See *Ex parte Forman*, 230 USPQ 546 (Bd. Pat. App. & Inter, 1986) and In *re Wands*, 8USPQ2d 1400 (Fed. Cir. 1988); these factors include the following:

The instant claims are drawn to an adenovirus designed to improve production of AAV vectors in which the Rep proteins are under control of an inducible promoter. As well the vector encodes Cap proteins under an inducible promoter. Previous experimentation has demonstrated that over-expression of Rep is detrimental to the cell. However, Cap over-expression provides a benefit in the production of AAV. Specifically, the adenovirus vector is designed to express Rep 78, 68, 52 and 48. The amino acid sequences for these proteins from AAV-2 are provided in SEQ ID NO:2, 4, 6 and 7 and the nucleic acid sequences in SEQ ID NO: 1, 3 and 5. The Cap proteins are VP-1, VP-2 and VP-3. The protein sequences from AAV-2 are provided in SEQ ID NO: 9-11 and the nucleic acid sequence in SEQ ID NO:8.

First, the claims are unclear as to whether the vector must encode Rep78 and 68 by notation of REP78/68 or REP 52 and 48 by notation REP52/48. For example, REP78/68 is an understandable notation for the genetic region as it is a single gene that encodes both REP 78 and 68. The transcript that results from this region is alternatively spliced to yield REP78 and 68. It appears the claim intends that the AAV can comprise REP 78, REP 68 or both REP78/68, there is some confusion in the overall claim language. For example, claim 4 recites that "an AAV REP78/68 polypeptide" can be REP 78, REP 68 or a combination thereof. As REP78 and REP68 are single peptide, the recitation "combination thereof" implies that the combination of the two is a fusion but such a reading of the claims is not supported by the specification. The situation is similar for REP52/48 notations.

Secondly, claims 5, 6, 8, 12, 16, 17, 19, 25-27 and 29 are drawn to a series of these molecules that are "substantially identical" or "substantially similar" to the nucleic acids (SEQ ID NO: 1, 3, 5 and 8) or the peptides themselves (SEQ ID NO: 2, 4, 6, 7 and 9-11). Furthermore, this analysis extends to hsp70 or a molecule that is substantially identical to SEQ ID NO:14. As guidance the specification teaches, "The term " substantially identical", as used herein to describe a degree of similarity between nucleotide sequences, refers to two or more sequences that have in one embodiment at least about least 60%, in another embodiment at least about 70%, in another embodiment at least about 80%, in another embodiment about 90% to about 99%, in another embodiment about 95% to about 99%, and in yet another embodiment about 99% nucleotide identity, when compared and aligned for maximum correspondence, as measured using one of the following sequence comparison algorithms (described herein below under the heading "Nucleotide and Amino Acid Sequence Comparisons" or by visual inspection." Specifically, these nucleic acid molecules can be those that are polymorphisms, mutagenized or sequences that hybridize substantially to the SEQ ID NO:s. These protein sequences are those that share three-dimensional structure, contain protein sequences that have functionally equivalent amino acids or are biologically equivalent molecules. The scope of claims 5, 6, 8, 12, 16, 17, 19, 25-27 and 29 is extremely broad in that molecules that are substantially identical or similar to SEQ ID NO:s 1-11 encompass a broad and potentially diverse genus. For example, considering those molecules that are substantially identical/similar to Rep78 or SEQ ID NO:1, the guidance in the specification directs one of skill in the art to look at the 3-d structure of proteins to identify those that would be biologically equivalent molecules (provide the same function) or to mutagenize any combination of residues to identify those that can tolerate any

change. In the later case, the protein is 535 amino acids which do not mean that mutational analysis is limited to mutation of 535 amino acids individually. Rather, the number of mutations that can be introduced is limitless and but the combination of mutations that would encompass an unlimited number of amino acids that could be mutated would exceed reasonable analysis and exceed millions of combinations). Furthermore, it is well known that Rep78 and Rep68 are required for AAV DNA replication and mediate multiple activities including the ability to bind to specific sites within the AAV terminal hairpin DNA, nick *trs,* DNA-DNA and DNA-RNA (54) helicase activity, ATPase activity as well as regulation of AAV and heterologous promoters, preferential integration of AAV genomes into a region on the q arm of human chromosome 19. For this protein it is not clear what if any activity is required of the resulting recited peptide.

Therefore, for each recited molecule of claims 5, 6, 8, 12, 16, 17, 19, 25-27 and 29 the specification provides a single sequence but recites this molecule in such broad terms that the structure-function requirement is not clear. In fact, by recitation of molecules that are substantially identical/similar molecules, the claims are drawn to any interpretation that would result in a substitute that either looks but doesn't function in the same manner or that functions in the same manner but does not share any structural properties with the disclosed sequences. The court and the Board have Repeatedly held (Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.,18 USPQ2d 1016 (CA FC, 1991); Fiers v. Revel, 25 USPQ2d 1601 (CA FC 1993); Fiddes v. Baird, 30 USPQ2d 1481 (BPAI 1993) and Regents of the Univ. Calif. v. Eli Lilly & Co., 43 USPQ2d 1398 (CA FC, 1997)) that an adequate written description of a nucleic acid/amino acid requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it, irrespective of the complexity or simplicity of the method; what is

required is a description of the nucleic acid itself. It is not sufficient to define DNA/protein solely by its principal biological property, because disclosure of no more than that, as in the instant case, is simply a wish to know the identity of any DNA/peptide with that biological property. Naming a type of material generically known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material. When one is unable to envision the detailed constitution of a complex chemical compound having a particular function, such as a nucleic acid, so as to distinguish it from other materials, as well as a method for obtaining it, conception has not been achieved until reduction to practice has occurred, i.e., until after the nucleic acid has been isolated. Thus, claiming all DNA or protein molecules that achieve a result without defining what means will do so is not in compliance with the description requirement. Rather, it is an attempt to preempt the future before it has arrived. Also, where a claim purports to cover all nucleic acids that encode a specific protein and the specification discloses but a single DNA known to do so, or all protein similar to a particular DNA or protein sequence the situation is analogous to a single means claim and does not meet the enablement requirement under para. 1 of §112. Furthermore, the ability to determine *a priori* whether a homologue or variant can function in the recited invention is not a high art. A particular protein sequence determines the protein's structural, and functional properties, and a predictability of a Representative number of claimed polypeptide sequences that display noteworthy biological properties requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e., expectedly intolerant to modification), and detailed knowledge of the ways in which a protein's structure relates to its functional usefulness (see Guo et al and Lesk et al). Therefore, the ability to

predict *a priori* which sequences that are identified following hybridization will meet a particular goal must be considered to be poorly developed.

Given the large size and diversity of the recited sequences, the absence of disclosed or art recognized correlations between structure and function and the large number of potential sequences or homologues, variants, and sequence isolated by hybridization, it must be considered that any sequence with the required activity or structure must be empirically determined. In view of predictability of the art to which the invention pertains and the lack of guidance in the specification: undue experimentation would be required to practice the claimed methods with reasonable expectation of success, absent a specific and detailed description in the specification. Given the above analysis of the factors which the courts have determined are critical in determining whether a claimed invention is enabled, it must be concluded that the skilled artisan would have had to have conducted undue unpredictable experimentation in order to practice the claimed invention.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1, 2, 4-9, 21, 22, 24-29 and 31 are rejected under 35 U.S.C. 102(b) as being anticipated by Lebkowski et al (US 5,354,678; see entire document).

Lebkowski et al teach construction of systems to produce AAV in which REP is under control of an inducible promoter (see e.g. col 13, line 17-21) wherein specifically an adenovirus vector encoding REP and CAP peptides (see e.g. col 14, line 59-68 and figure 5-7). Absent evidenced to the contrary REP 78, 68, 52 and 48 as well as VP-1, VP-2 and VP3 are encoded by the adenovirus as recited in claims 1, 2, 4, 7, 21-24, 29 and 31 and can be considered to be substantially similar or identical to SEQ ID NO:s:2, 4, 6, 7 and 9-11 (amino acid) and the nucleic acid sequences in SEQ ID NO: 1, 3, 5 and 8 since they perform the same function and have the same 3-d structures. The promoter can be MMTV or MT, which are induced by in the broadest interpretation chemicals as recited in claim 9.

Claims 1-10, 13-29 and 31 are rejected under 35 U.S.C. 102(e) as being anticipated by Pericaudet et al, (US 6,420,170 see entire document) or alternatively 102(b) as being anticipated by Pericaudet et al (WO 97/00947; see entire document).

Pericaudet et al teach construction of a recombinant adenovirus vector (rAd) comprised of AAV rep 78 and rep 68 under control of a tetracycline inducible promoter (see e.g. col 9, line 49-col 10, line 4 and example 2) wherein AAV is AAV2. The REP and CAP proteins are absent evidence to the contrary substantially similar or identical to SEQ ID NO:s:2, 4, 6, 7 and 9-11 (amino acid) and the nucleic acid sequences in SEQ ID NO: 1, 3, 5 and 8 since they perform the same function and have the same 3-d structures. REP 52 and 48 are under the control of their

endogenous p19 promoter, which is constitutive. The CAP sequence is under control of their p40 promoter, which is constitutive.

Claims 1, 2, 4-9, 13-19, 21, 22, 24-31 are rejected under 35 U.S.C. 102(e) as being anticipated by Wadsworth et al, (US 2002/0045250 see entire document).

Wadsworth et al teach construction of a recombinant adenovirus vector (rAd) comprised of an AAV rep protein under control of an inducible promoter (see e.g.) and CAP is under control of CMV (see e.g. figure 7, col 8, bridging ¶ col 7-8, line 35- col 9, line 10). The promoter can be MMTV or MT, which are induced by in the broadest interpretation chemicals as recited in claim 9. The REP and CAP proteins are absent evidence to the contrary substantially similar or identical to SEQ ID NO:s:2, 4, 6, 7 and 9-11 (amino acid) and the nucleic acid sequences in SEQ ID NO: 1, 3, 5 and 8 since they perform the same function and have the same 3-d structures. In a single embodiment, p5 is replaced with an inducible promoter, p19 is retained and p40 is replaced with CMV (similar to figure 7 in combination with embodiments disclosed in the specification).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-31 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lebkowski et al (US 5,354,678; see entire document) or Pericaudet et al, (US 6,420,170 see entire document) see entire document) or Wadsworth et al, (US 2002/0045250 see entire document) in view of Moonen et al (WO/1998/006864; however the rejection is based upon US 7,186,698, which is the US publication of WO/1998/006864; see entire document).

Applicants claim a recombinant adenovirus that encodes REP78/68 under an inducible promoter wherein the inducible promoter is hsp70 or substantially similar to SEQ ID NO:14.

The teachings of Lebkowski et al, Pericaudet et al and Wadsworth et al are described above and are applied as before except none of the references teach that the inducible promoter is hsp70.

Moonen et al teach that hsp promoter is successfully activated *in vivo* using ultrasound controlled by MRI (see e.g. abstract). For example, hsp70 can be inserted into an adenoviral vector to control express of desired genes (see e.g. figure 2). The promoter is also useful for expressing toxic genes in a controllable environment (col 4, line 1-5). The promoter is preferable for spatial and temporal regulation of gem expression by the use of focused ultrasound (see e.g. col 1, line 21-29). Absent evidence to the contrary, the promoters of Moonen et al are substantially identical to SEQ ID NO:14.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the inducible promoter taught by of Lebkowski et al, Pericaudet et al and Wadsworth et al with the hsp70 promoter taught by Moonen et al because of Lebkowski et al, Pericaudet et al and Wadsworth et al teach that it is within the ordinary skill of the art to express rep under control of an inducible promoter in an adenoviral construct and because Moonen et al

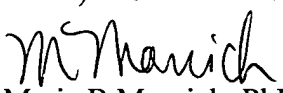
teach that it is within the ordinary skill of the art to use hsp70 as an inducible promoter in a recombinant vector such as adenovirus. One would have been motivated to do so in order to receive the expected benefit of expression of toxic genes in a controllable environment with spatial and temporal regulation of gene expression by the use of focused ultrasound. Based upon the teachings of the cited references, the high skill of one of ordinary skill in the art, and absent evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maria B. Marvich, PhD whose telephone number is (571)-272-0774. The examiner can normally be reached on M-F (7:00-4:00).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach, PhD can be reached on (571)-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.



Maria B Marvich, PhD
Examiner
Art Unit 1633